Clinical trial results:
A Multicenter Phase 2 Open-Label, Single-Arm, Prospective, Interventional Study of Plasma-Derived Factor VIII/VWF (Alphanate®) in Immune Tolerance Induction Therapy in Subjects with Congenital Hemophilia A

Summary

EudraCT number	2015-005524-26
Trial protocol	ES IT
Global end of trial date	18 September 2020

Results information

Result version number	v1 (current)
This version publication date	02 October 2021
First version publication date	02 October 2021

Trial information

Trial identification

Sponsor protocol code	GBI1406

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03095287
WHO universal trial number (UTN)	-
Other trial identifiers	IND/CTA Number: 016703

Notes:

Sponsors

Sponsor organisation name	Grifols Biologicals LLC
Sponsor organisation address	5555 Valley Boulevard, Los Angeles, United States, CA 90032
Public contact	Rhonda Griffin, Grifols Therapeutics LLC, +1 919 316 6693, Rhonda.griffin@grifols.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to assess the percentage of subjects who achieve complete immune tolerance within 33 months of initiating Alphanate for immune tolerance induction (ITI) and to assess the safety of Alphanate treatment for ITI.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 2
Worldwide total number of subjects	2
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	2
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at two sites in India from 03 January 2018 (first subject enrolled to receive the study drug) to 18 September 2020 (last subject completed).

Pre-assignment

Screening details:

Male subjects with diagnosis of Congenital Hemophilia A were enrolled in a single arm to receive alphanate. The study was to be conducted in 2 phases: Immune Tolerance Induction Phase followed by Prophylactic Phase. However, due to the limited enrollment, the study was terminated prior to the start of Prophylactic Phase.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Alphanate

Arm description:

Subjects entered the immune tolerance induction (ITI) phase and received alphanate IV at a starting dose of 100 IU/kg/day. Dose could be uptitrated to 200 IU/kg/day based on investigator's discretion. The maximum duration of treatment was 32 months and 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Alphanate
Investigational medicinal product code	
Other name	Plasma Derived Factor VIII/von Willebrand Factor
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Alphanate IV daily until complete immune tolerance was achieved or for 33 months if complete immune tolerance was not achieved. Alphanate was administered 100 International units (IU)/kg/day for at least 90 days during ITI phase. After the first 90 days, dose could be increased to 200 IU/kg/day if there was <20% decrease in inhibitor titer or an increase in the rate of bleeding events relative to the rate of bleeding events experienced during the first 90 days of treatment, or if the inhibitor increased to >500 Bethesda Units (BU), after initiation of Alphanate ITI treatment.

Number of subjects in period 1	Alphanate
Started	2
Completed	0
Not completed	2
Adverse Event	1
Treatment Failure	1

Baseline characteristics

Reporting groups	
Reporting group title	Alphanate
Reporting group description:	
Subjects entered the immune tolerance induction (ITI) phase and received alphanate IV at a starting dose of 100 IU/kg/day. Dose could be uptitrated to 200 IU/kg/day based on investigator's discretion. The maximum duration of treatment was 32 months and 2 weeks.	

Reporting group values	Alphanate	Total	
Number of subjects	2	2	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	2	2	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Due to low number of participants enrolled in the study 0 participants are reported to maintain participant confidentiality.			
Units: Subjects			
Female	0	0	
Male	2	2	

End points

End points reporting groups

Reporting group title	Alphanate

Reporting group description:

Subjects entered the immune tolerance induction (ITI) phase and received alphanate IV at a starting dose of 100 IU/kg/day. Dose could be uptitrated to 200 IU/kg/day based on investigator's discretion. The maximum duration of treatment was 32 months and 2 weeks.

Primary: Percentage of Subjects who Achieved Complete Immune Tolerance Within 33 Months of Initiation of Immune Tolerance Induction (ITI) Treatment Phase

End point title	Percentage of Subjects who Achieved Complete Immune Tolerance Within 33 Months of Initiation of Immune Tolerance Induction (ITI) Treatment Phase[1]

End point description:

Complete immune tolerance was defined as the participants achieving 2 consecutive undetectable inhibitor titers (<0.6 BU) performed within 2 weeks of each other, Factor VIII activity (FVIII:C) in vivo plasma recovery ≥66% of the predicted normal value and FVIII:C half-life ≥6 hours after a 72-hour FVIII treatment-free period.

End point type	Primary

End point timeframe:

Up to 32.5 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for this outcome measure was not collected and analysed, as the study was terminated early by the sponsor due to limited enrollment (non-safety related decision).

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: number				
number (not applicable)				

Notes:

[2] - The data was not analysed as the study was terminated by sponsor due to limited enrollment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved Either Complete or Partial Immune Tolerance Within 33 Months of Initiation of ITI Treatment Phase

End point title	Percentage of Subjects who Achieved Either Complete or Partial Immune Tolerance Within 33 Months of Initiation of ITI Treatment Phase

End point description:

Complete immune tolerance was defined as the participants achieving 2 consecutive undetectable inhibitor titers (<0.6 BU) performed within 2 weeks of each other, Factor VIII activity (FVIII:C) in vivo plasma recovery ≥66% of the predicted normal value and FVIII:C half-life ≥6 hours after a 72-hour FVIII treatment-free period. Partial immune tolerance was defined as participants achieving reduction of inhibitor titer to <5 BU confirmed at 2 consecutive assessments within 2 weeks of each other, FVIII:C in vivo plasma recovery of <66% of the predicted normal value or FVIII:C half-life of <6 hours after a 72-hour FVIII treatment-free period and clinical response to FVIII therapy. Data for this outcome measure

was not collected and analysed, as the study was terminated early by the sponsor due to limited enrollment (non-safety related decision).

End point type	Secondary

End point timeframe:

Up to 32.5 months

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: number				
number (not applicable)				

Notes:

[3] - The data was not analysed as the study was terminated by sponsor due to limited enrollment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved Complete or Partial Immune Tolerance Without Relapse During the Prophylactic Phase

End point title	Percentage of Subjects who Achieved Complete or Partial Immune Tolerance Without Relapse During the Prophylactic Phase

End point description:

Relapse during the prophylactic phase for participants who have achieved complete immune tolerance was defined as a return of FVIII inhibitor titer to detectable levels (≥0.6 BU) or FVIII:C recovery <66% of the predicted normal value or FVIII:C half-life <6 hours, confirmed by repeat assessment within approximately 2 weeks. Relapse for participants who have achieved partial immune tolerance was defined as an increase of FVIII inhibitor titer to ≥5 BU, confirmed by repeat assessment within approximately 2 weeks. Data for this outcome measure was not collected and analysed, as the study was terminated early by the sponsor due to limited enrollment (non-safety related decision).

End point type	Secondary

End point timeframe:

12 months during prophylactic phase

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: number				
number (not applicable)				

Notes:

[4] - The data was not analysed as the study was terminated by sponsor due to limited enrollment.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeding Events During ITI Treatment Phase and Prophylactic Phase

End point title	Number of Bleeding Events During ITI Treatment Phase and Prophylactic Phase

End point description:

This study was terminated, and the data is not reported for this outcome measure to main participant's confidentiality.

End point type	Secondary

End point timeframe:

Up to 32.5 months

End point values	Alphanate			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: number				
number (not applicable)				

Notes:

[5] - Study was terminated, the data is not reported for this endpoint to maintain subject confidentiality

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 32.5 months	
Adverse event reporting additional description:	
Safety population included all subjects who received any amount of Alphanate.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Alphanate
Reporting group description:	
Subjects entered the immune tolerance induction (ITI) phase and received alphanate IV at a starting dose of 100 IU/kg/day. Dose could be uptitrated to 200 IU/kg/day based on investigator's discretion. The maximum duration of treatment was 32 months and 2 weeks.	

Serious adverse events	Alphanate		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatitis C Antibody positive			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural hemorrhage			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Alphanate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	2		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Pyrexia			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	8		
Musculoskeletal and connective tissue			

disorders Pain in extremity subjects affected / exposed occurrences (all)	 1 / 2 (50.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) Varicella subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 1 / 2 (50.00%) 1 1 / 2 (50.00%) 2 1 / 2 (50.00%) 1 1 / 2 (50.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2016	The purpose of the amendment was to add synopsis, visits were changed from every month to Weeks 2, 4, 6, and 8 and monthly thereafter, inclusion criterion was changed to restrict range of inhibitor titer levels to > 0.6 BU and < 10 BU at Screening, exclusion criteria was changed to allow for previous use of treatments prohibited during the study (i.e., immunosuppressive drugs azathioprine, cyclophosphamide, high-dose immunoglobulin, interferon, or protein A column or plasmapheresis) prior to study enrolment, requirement to discontinue subjects who experience an interruption of ITI treatments for > 2 weeks, who receive < 80% of prescribed ITI treatment over a continuous 8-week period, or who experience a relapse during the Prophylactic Phase of the study was removed, assessment was added of FVIII:C in vivo recovery and if FVIII:C in vivo recovery is ≥ 66%, that separate visits will be needed to perform the FVIII:C half-life assessment.
20 December 2016	The purpose of the amendment was to add 2-hour time window at the 12-hour timepoint when sampling for FVIII:C half-life, immunosuppressive treatment initiated after inhibitor diagnosis will be collected under baseline characteristics was added.
21 March 2019	The purpose of the amendment was to increase participating sites from 20 to 30, emicizumab was added as a permitted concomitant medication.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 September 2020	The study was terminated by the sponsor in September 2020 due to limited enrolment (non-safety-related decision).	-

Notes:

Limitations and caveats

None reported